Br. J. clin. Pharmac. (1978), **5**, 243–247

BUMETANIDE AND FRUSEMIDE: A COMPARISON OF DOSE-RESPONSE CURVES IN HEALTHY MEN

L.E. RAMSAY, G.T. McINNES, J. HETTIARACHCHI, J. SHELTON & P. SCOTT
Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow, G11 6NT

1 Log dose-responses for the loop diuretics bumetanide and frusemide in healthy subjects deviated significantly from parallelism as regards urine volume and sodium excretion. Ignoring the non-parallelism the best estimate of natriuretic potency (bumetanide : frusemide) was 46 : 1 in the bumetanide dose range 0.5–2 mg.

2 For a given natriuresis the urinary potassium excretion following bumetanide was significantly lower than that for frusemide within this dose range.

3 The data illustrate the limitations of studies comparing diuretics at a single dose level. Extrapolation of the observed log dose-response curves provides one possible explanation for the relative potency (bumetanide : frusemide) of 20 : 1 reported when the drugs are used at high dosage in patients with renal failure.

Introduction

Bumetanide is a metanilamide derivative with potent diuretic activity (Feit, 1971) and therapeutic efficacy broadly similar to that of frusemide (Brogden, Speight & Avery, 1975; Drug and Therapeutics Bulletin, 1974; Lancet, 1975). From the results of comparative studies in healthy subjects and patients (Asbury, Gatenby, O'Sullivan & Bourke, 1972; Olesen, Sigurd, Steiness & Leth, 1973; Davies, Lant, Millard, Smith, Ward & Wilson, 1974; Murdoch & Auld, 1975) its potency relative to frusemide has been accepted as 40:1 in clinical practice (Drug and Therapeutics Bulletin, 1974; Lancet, 1975). When bumetanide and frusemide were compared at high dosage in patients with chronic renal failure the results were not consistent with a relative potency of 40:1, and suggested a potency (bumetanide : frusemide) of 20:1 (Allison, Lindsay & Kennedy, 1975; Kampf, 1975; Berg, Tromsdal & Wideroe, 1976). The pharmacological properties of bumetanide and frusemide may differ slightly and in particular there are reports that potassium excretion, for a given natriuresis, was less after bumetanide in healthy subjects (Branch, Read, Levine, Vander Elst, Shelton, Rupp & Ramsay, 1976) and in patients undergoing open heart surgery (Dunn, Kerr, McQueen & Thomson, 1975).

Parallel line bioassays of diuretics have been performed in animals for many years (Lipschitz, Hadidian & Kerpcsar, 1943) and have been used to study diuretics in healthy humans (Ford, Spurr & Moyer, 1957) and patients with heart failure (Greiner & Gold, 1952). The method allows stringent comparison of the dose-response curves of diuretics, can bring out subtle qualitative differences very clearly (Ramsay, Harrison, Shelton & Tidd, 1975), and provides an accurate quantitative estimate of relative potency. The dose-response curves for bumetanide and frusemide have been compared only approximately in man (Asbury *et al.*, 1972; Davies *et al.*, 1974) and in dogs (Ostergaard, Magnussen, Nielsen, Eilertsen & Frey, 1972; Frey, 1975). The aim of the present study was to define and compare their dose-response curves in healthy men.

Methods

Twelve healthy males aged 22–40 years consented to participate in the study. They were ambulant, avoided all medication for the duration of the study, and took no alcohol or caffeine containing drinks during test periods.

The six treatments were bumetanide 0.5 mg, 1 mg and 2 mg, and frusemide 20 mg, 40 mg and 80 mg. Tablets available commercially (Lasix, Hoechst, 20 mg and Burinex, Leo, 1 mg) were used and were prescribed open-label. All laboratory analyses were performed without knowledge of the treatment given.

All subjects took each of the six treatments on a single occasion in the course of the study, with an interval of at least 1 week between each treatment. The order of medication was allotted in random fashion, but to conform with a balanced study design consisting of two William's squares (Cochran & Cox, 1957).

On each test day a light breakfast, constant within subjects, was taken at 08.00 h after fasting overnight. At 09.00 h venous blood was taken, 500 ml tapwater

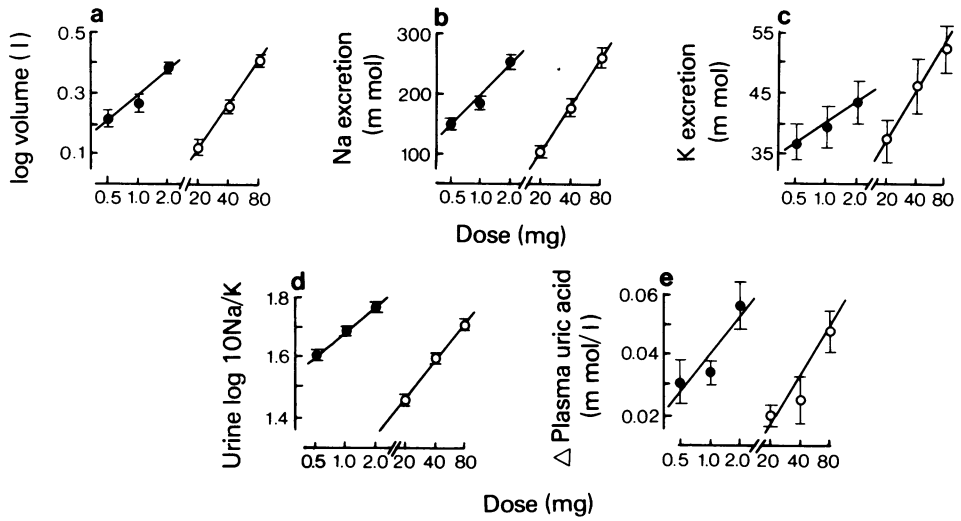

Figure 1 Log dose-response curves for bumetanide (●) and frusemide (○) with log volume (a), sodium excretion (b), potassium excretion (c), urine log 10 Na/K (d) and △ plasma uric acid (e) as responses. Mean (± s.e. mean) results for twelve subjects

was given orally, the bladdder was emptied, and the dose of diuretic indicated by the random table was taken by mouth. All urine passed from 09.00–15.00 h was collected. This 6 h period encompasses the full duration of activity of both diuretics (Davies *et al.*, 1974; Branch *et al.*, 1976). Further tapwater (500 ml) was taken at 11.00 h, and lunch (constant within subjects) was eaten at 13.00 h. A second venous blood sample was drawn at 15.00 h, at the end of the urine collection period.

Sodium and potassium concentration in plasma and urine were measured by flame photometry using lithium as the internal standard. The other biochemical analyses were performed by routine automated methods. There were no significant treatment-related changes in plasma sodium and potassium, in serum urea, creatinine, chloride or bicarbonate, or in urinary creatinine excretion, and the results for these variables have not been presented.

The analysis of variance was used to investigate whether the log dose-response trends deviated significantly from linearity ($P < 0.1$), and whether the slopes were significant ($P < 0.05$). The log-dose responses for the two drugs were tested to determine whether they deviated from parallelism ($P < 0.1$), and, where appropriate, the relative potency of the two drugs, with 95% confidence limits, was calculated (Armitage, 1971). The log dose-urine volume responses for each drug tended to deviate from linearity ($P < 0.1$ for each drug) and urine volume was log transformed to render the responses linear (Armitage, 1971). The urine Na/K ratio was log transformed to stabilize the variance of the responses (Armitage, 1971). Changes in plasma uric acid were calculated by subtracting the 09.00 h result from the 15.00 h result.

Results

Urine volume

The log dose-responses for urine volume (log transformed) did not deviate from linearity ($P > 0.1$ for each drug), and their slopes differed highly significantly from zero ($P < 0.001$ for each drug) (Figure 1a). The log dose-responses for the two drugs were significantly non-parallel ($P = 0.001$). This precluded calculation of a single estimate of relative potency which would be valid at all dose levels. Ignoring the non-parallelism, the best estimate of relative potency (bumetanide : frusemide) was 46:1. This is an approximate estimate of the relative potency of the two drugs which applies only in the dose range tested, i.e. bumetanide 0.5–2 mg and frusemide 20–80 mg.

Sodium excretion

For each diuretic the log dose-responses were consistent with linearity ($P > 0.1$) and highly significant ($P < 0.001$) (Figure 1b). The log dose-responses again deviated significantly from parallelism ($P < 0.025$). Ignoring the non-parallelism, the best overall estimate of relative potency (bumetanide : frusemide) was 46:1, with 95% confidence limits from 39:1 to 56:1. Again this estimate is an overall approximation, valid only in the

dose ranges tested. In view of the non-parallelism it is appropriate to consider potency estimates at various dose levels of either drug, and these were calculated for bumetanide (Table 1). As regards sodium excretion, 0.5 mg of bumetanide was equivalent to 28.7 mg frusemide (relative potency 57:1), and 2 mg bumetanide was equivalent to 71.6 mg frusemide (relative potency 36:1). Estimates of the potency of the two drugs at dose levels outwith the range tested in the experiment were calculated by extrapolating from the observed log dose-response curves, and are also shown in Table 1. The validity of these estimates is discussed later. The predicted potency of bumetanide relative to frusemide fell from 92:1 for bumetanide (0.125 mg) to 21:1 for bumetanide (10 mg).

Potassium excretion

The log dose-response trends for the two drugs did not deviate from linearity ($P > 0.1$). There was a highly significant log dose-response after frusemide ($P < 0.001$), whereas the slope for bumetanide was not significantly different from zero ($P < 0.1$). The average log dose-resonse for the two drugs was significant ($P < 0.001$), justifying continuation of the analysis. Although the log dose-responses for the two drugs appeared non-parallel (Figure 1c), this was not statistically significant ($P > 0.1$). The relative potency (bumetanide : frusemide) for potassium excretion was 21:1, with 95% confidence limits from 7:1 to 38:1. These confidence limits did not overlap those for the overall estimate for sodium excretion (lower confidence limit for sodium excretion 39:1; upper confidence limit for potassium excretion 38:1). In the dose range examined the potency of bumetanide in promoting potassium excretion was therefore significantly lower than its natriuretic potency, when compared to frusemide.

Urine log 10 Na/K ratio

The log dose-responses were highly significant ($P < 0.001$ both drugs) and did not deviate from parallelism ($P > 0.1$) (Figure 1d). The relative potency (bumetanide : frusemide) was 78:1. The 95% confidence limits for this estimate (55:1 to 127:1) overlapped those for sodium excretion only marginally.

Plasma uric acid

Dose-related increases in plasma uric acid over the 6 h period were significant ($P < 0.005$ for each drug) and parallel ($P > 0.1$) (Figure 1e). The relative potency (bumetanide : frusemide) was 65:1. The confidence limits for this estimate overlapped those for overall sodium excretion clearly (Table 1), indicating that the potency of the two diuretics in elevating plasma uric acid was not dissociated significantly from their natriuretic potency.

Discussion

The diuretics were compared at doses usually prescribed in oedematous states, and *in this dose-range* the non-parallelism of the log dose-responses for urine volume and sodium excretion probably has no practical importance. Thus it seemed justifiable to proceed to estimate the relative potency of the two

Table 1 Best estimates of the relative potency bumetanide : frusemide using different response parameters, with 95% confidence limits where appropriate

Response parameter	*Bumetanide dose level (mg)*	*Frusemide equivalent (mg)*	*Relative potency bumetanide : frusemide*	*95% confidence limits*
Urine log volume*	0.5–2	20–80	46:1	39:1–56:1
Sodium excretion*	0.5–2	20–80	46:1	39:1–56:1
Potassium excretion	0.5–2	20–80	21:1	7:1–38:1
Urine log 10 Na/K	0.5–2	20–80	78:1	55:1–127:1
Δ Plasma uric acid	0.5–2	20–80	65:1	39:1–136:1
Sodium excretion**	0.125	12	92:1	—
Sodium excretion	0.5	28.7	57:1	—
Sodium excretion	2	71.6	36:1	—
Sodium excretion**	5	130	26:1	—
Sodium excretion**	10	207	21:1	—

* Significant non-parallelism was ignored in calculating relative potency estimates, which are valid only within the dose ranges stated.

** Estimates of frusemide equivalence and relative potency obtained by extrapolation of the observed log dose-response curves. Their validity rests on the untested assumption that linearity holds beyond the points defined experimentally.

drugs. The estimates for log volume and sodium excretion were identical at 46:1, and agreed with the accepted estimate of 40:1 (Drug and Therapeutics Bulletin, 1974; Lancet, 1975). However the non-parallelism suggests that this relative potency will not hold over a wider dose-range. Extrapolation from the data (Table 1) needs to be viewed with caution, but provides a possible explanation for the lower potency of bumetanide (20:1) when used at doses of 5–10 mg in chronic renal failure (Allison *et al.*, 1975; Kampf 1975; Berg *et al.*, 1976). The fall in relative potency with increasing dose may therefore be a function of the intrinsic activity of the drugs, and not of the disease state. Possible explanations for the non-parallelism include non-linear kinetics for one of the drugs, an action on different renal receptors, or a dissimilar action on a common receptor, but at present there is insufficient information to distinguish between these alternatives.

The significant dissociation of potency estimates for sodium excretion and potassium excretion confirms the suggestion that bumetanide causes less potassium loss than frusemide, for a given natriuresis, in healthy subjects (Branch *et al.*, 1976). Although potassium homeostasis in disease states is influenced greatly by factors other than the diuretic itself, the clinical relevance of this observation is supported by one study (Dunn *et al.*, 1975) and, as pointed out by Branch *et al.* (1976), by data from another (Asbury *et al.*, 1972). Bumetanide may have a slight advantage over frusemide for patients in whom potassium loss is particularly undesirable, e.g. in those with chronic liver disease. Potassium excretion by healthy subjects in response to diuretics has been related to *in vitro* carbonic anhydrase inhibition (Puschett & Rastegar, 1974). In this respect frusemide has significant activity (Puschett & Rastegar, 1974) whereas that of bumetanide is weak (Lant, 1975), and the findings for potassium excretion may possibly be due to this.

Accurate knowledge of the relative potency of diuretics makes it possible to administer them in proper doses and provides a background against which their toxic and other pharmacologic properties can be evaluated fairly (Greiner & Gold, 1952). It is particularly important when there seems little to choose between two drugs, as in the case of bumetanide and frusemide. Comparisons of diuretics at a single dose level for each drug give impressions of diuretic potency which, without knowing the slopes of the dose-responses, have an indeterminate error (Greiner, Gold, Bliss, Gluck, Marsh, Mathes, Modell, Otto, Kwitt & Warshaw, 1951). Estimates of relative potency obtained in such studies are frequently assumed to be valid over a range of doses, an assumption which requires parallelism of the log dose-responses. The results of the present study clearly show that this assumption cannot be justified. Methods for comparing the log dose-responses of new diuretics with those of a standard drug are simple and accurate, and should be applied at an early stage in the evaluation of any new drug.

We acknowledge the technical assistance of Mr Kenneth McElroy and Mr Michael Walker, and the staff of the Biochemistry Department of the Western Infirmary and Gartnavel General Hospital. Financial assistance was kindly provided by Leo Laboratories. L.E.R. is a Searle Research Fellow in Clinical Pharmacology. We thank the volunteers who participated in the study. Reprint requests should be addressed to L.E.R.

References

ALLISON, M.E.M., LINDSAY, M.K. & KENNEDY, A.C. (1975). Oral bumetanide in chronic renal failure. *Postgrad. med. J.*, **51**, Suppl. 6, 47–50.

ARMITAGE, P. (1971). *Statistical methods in medical research.* Oxford: Blackwell Scientific Publications.

ASBURY, M.J., GATENBY, P.B.B., O'SULLIVAN, S. & BOURKE, E. (1972). Bumetanide: potent new "loop" diuretic. *Br. med. J.*, **1**, 211–213.

BERG, K.J., TROMSDAL, A. & WIDEROE, T.-E. (1976). Diuretic action of bumetanide in advanced chronic renal insufficiency. *Eur. J. clin. Pharmac.*, **9**, 265–275.

BRANCH, R.A., READ, P.R., LEVINE, D., VANDER ELST, E., SHELTON, J., RUPP, W. & RAMSAY, L.E. (1976). Furosemide and bumetanide: a study of responses in normal English and German subjects. *Clin. Pharmac. Ther.*, **19**, 538–545.

BROGDEN, R.N., SPEIGHT, T.M. & AVERY, G.S. (1975). Bumetanide: a preliminary report of its pharmacological and therapeutic efficiency in oedema. *Drugs*, **9**, 4–18.

COCHRAN, W.G. & COX, G.M. (1957). *Experimental Designs*, pp. 133–135. New York: Wiley.

DAVIES, D.L., LANT, A.F., MILLARD, N.R., SMITH, A.J., WARD, J.W. & WILSON, G.M. (1974). Renal action, therapeutic use, and pharmacokinetics of the diuretic bumetanide. *Clin. Pharmac. Ther.*, **15**, 141–155.

DRUG AND THERAPEUTICS BULLETIN. (1974). New diuretics – bumetanide and metolazone. **12**, 49–51.

DUNN, F.G., KERR, I.C., McQUEEN, M.J. & THOMSON, R.M. (1975). Comparison of intravenous bumetanide and frusemide during open heart surgery. *Postgrad. med. J.*, **51**, Suppl. 6, 72–76.

FEIT, P.W. (1971). Aminobenzoic acid diuretics. 2. 4-Substituted-3amino-5-sulfamylbenzoic acid derivatives. *J. med. Chem.*, **14**, 432–439.

FORD, R.V., SPURR, C.L. & MOYER, J.H. (1957). The problem of bioassay and comparative potency of diuretics. 1. Parenteral and oral mercurial diuretics. *Antibiot. Med. clin. Ther.*, **4**, 708–724.

FREY, H.H. (1975). Pharmacology of bumetanide. *Postgrad. med. J.*, **51**, Suppl. 6, 14–18.

GREINER, T. & GOLD, H. (1952). The clinical assay of diuretic agents. 1. Biologic considerations which determine the design. *Biometrics*, **8**, 232–247.

GREINER, T., GOLD, H., BLISS, C.I., GLUCK, J., MARSH, R., MATHES, S.B., MODELL, W., OTTO, H., KWIT, N.T. & WARSHAW, L. (1951). Bioassay of diuretic agents in patients with congestive failure. *J. Pharmac. exp. Ther.*, **103**, 431–440.

KAMPF, D. (1975). In Discussion. *Postgrad. med. J.*, **51**, Suppl. 6, 53.

LANCET. (1975). Bumetanide. *Lancet*, **ii**, 860.

LANT, A.F. (1975). Effects of bumetanide on cation and anion transport. *Postgrad. med. J.*, **51**, Suppl. 6, 35–42.

LIPSCHITZ, W.L., HADIDIAN, Z. & KERPCSAR, A. (1943). Bioassay of diuretics. *J. Pharmac. exp. Ther.*, **79**, 97–110.

MURDOCH, W.R. & AULD, W.H.R. (1975). Bumetanide – acute and long term studies of a new high potency diuretic. *Postgrad. med. J.*, **51**, 10–14.

OLESEN, K.H., SIGURD, B., STEINESS, E. & LETH, A. (1973). Bumetanide, a new potent diuretic. *Acta med. Scand.*, **193**, 119–131.

OSTERGAARD, E.H., MAGNUSSEN, M.P., NIELSEN, C.K., EILERTSEN, E. & FREY, H.-H. (1972). Pharmacological properties of 3-n-butylamino-4-phenoxy-5-sulfamyl-benzoic acid (bumetanide), a new potent diuretic. *Arzneimittel-Forsch.*, **22**, 66–72.

PUSCHETT, J.B. & RASTEGAR, A. (1974). Comparative study of the effects of metolazone and other diuretics on potassium excretion. *Clin. Pharmac. Ther.*, **15**, 397–405.

RAMSAY, L., HARRISON, I., SHELTON, J. & TIDD, M. (1975). Relative potency of prorenoate and spironolactone in normal man. *Clin. Pharmac. Ther.*, **18**, 391–400.

(Received May 19, 1977)